POLICY AND COMMUNICATIONS BULLETIN
THE CLINICAL CENTER

Medical Administrative Series

M92-5 (rev.) 26 September 2000

MANUAL TRANSMITTAL SHEET

SUBJECT: Research Involving Children and Children's Assent to Research

1. Explanation of Material Transmitted: This issuance transmits the Clinical Center's policy regarding research involving children and children's assent to that research, and the route by which certain proposed studies are sent to the Secretary, DHHS. The policy was reviewed by the Medical Executive Committee on 19 September 2000 and approved with changes.

2. Material Superseded: MAS No. M92-5 (rev.), dated 15 July 1997

3. Filing Instructions: Informed Consent Section

   Remove: No. M92-5 (rev.), dated 15 July 1997

   Insert: No. M92-5 (rev.), dated 26 September 2000

DISTRIBUTION

Physicians, Dentists and Other Practitioners Participating in Patient Care

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and Children's Assent to Research

A. PURPOSE

Not only does the law generally deny children the right to give legally valid consent to participate in biomedical or behavioral research, but their role as research participants may be inherently compromised by a limited ability to comprehend the risks and consequences of such participation. This vulnerable position creates the moral obligation to afford extra protections to every child who is a research subject.

This issuance provides guidance on additional safeguards for the protection of children involved in biomedical and behavioral research, and is consistent with Federal Regulations for the Protection of Human Subjects, Subpart D - Additional Protections for Children Involved as Subjects in Research - 45 CFR 46.401-409 (available from the Department of Clinical Bioethics, 496-2429).

B. DEFINITIONS

Children are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under applicable law of the jurisdiction in which the research will be conducted. Generally, the law considers any person under 18 years old to be a child.

Assent means a child's affirmative agreement to participate in research. Mere failure to object should not be construed as assent. Assent can be given only following a discussion between the

investigator, child and parent/guardian (when appropriate) incorporating the types of information currently required for informed consent, in language appropriate to the child's level of understanding.

Permission means the agreement of parent(s) or guardians(s) to the participation of their child or ward in research. Valid permission can be given only following an explanation incorporating the information currently required for informed consent.

Parent means a child's biological or adoptive parent.

Guardian means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care for the child.

Risk is the probability of harm (physical, emotional, social, or economic). The probability of harm may vary from minimal to substantial. In determining potential harms to research subjects it is necessary to consider not only objectively quantifiable data (e.g., potential for infection, calculable loss of income), but also other aspects of the research study which may weigh in a negative fashion in the research participant's decision making process. For example, a procedure which carries very low medical risks but substantial social risks is drawing blood for HIV testing (and obtaining positive results). These negative aspects can be called burdens. Burdens may encompass both medical and non-medical aspects of a research project, and they should not be viewed as limited to either category.

Minimal Risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. For example, the risk to a healthy person of taking a treadmill test is no greater than a brisk walk or jog.

Benefit is a valued or desired outcome. In research, the primary benefit intended is the acquisition of knowledge that may eventually lead to improved medical care, health status, or quality of life. The improvement of health may also be an immediate benefit of research. When a newly developed drug is shown to be a useful therapy, this implies that the health of some research subjects improved as a result of receiving the drug. The same holds true for

behavioral research designed to evaluate new modes of treatment for behavioral or cognitive disorders -- or even for physical problems (e.g., relief of chronic pain through hypnosis). It is important, however, to keep in mind that the primary benefit of research is new knowledge that may lead to improvements in health care for persons other than the subjects.

Advocate is an individual appointed by the Institutional Review Board (IRB), or through procedures approved by it, to act in the best interests of a child who is a ward of the State, other agency, institution or entity.

C. POLICY ON RESEARCH INVOLVING CHILDREN

1. Duties of an IRB when children are involved as research subjects.

An IRB may approve research involving children only if it has determined that:

(a) the research is scientifically sound and significant;

(b) in keeping with ethical guidelines on research involving children, when appropriate, earlier studies have been conducted first on animals and adult humans, and then on older children before involving younger children and infants. Investigators and IRBs are responsible for giving ethical and scientific justifications for enrolling children within the age range stipulated in the protocol;

(c) risks to children are minimized using the safest procedures consistent with sound research design and, whenever feasible, using procedures performed for diagnostic or treatment purposes;

(d) adequate provisions are made to protect the privacy of children and their parents or guardians, and to maintain the confidentiality of data;

(e) subjects will be selected in an equitable manner; and

(f) the conditions of all other applicable sections of this policy

are met.

2. The federal regulations permit four categories of research involving children [see (a)-(d), below]. Each category involves a different degree of risk and prospect of benefit to the child. Each category imposes special requirements upon the IRB's reviews of any protocols involving children. However, for any protocol involving children, the IRB, in consultation with the Principal Investigator, is responsible for determining into which of the four categories of research the study belongs and documenting in the minutes its rationale for this choice.

(a) Category 1: Research Not Involving Greater than Minimal Risk (45 CFR 46.404)

Research that does not involve greater than minimal risk to children may be conducted provided an IRB has determined that:

(i) the conditions of section C-1 (above) are met; and

(ii) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in section C-3 (below).

An example of research in this category is the collection of normally voided urine samples for research analysis.

(b) Category 2: Research Involving Greater than Minimal Risk but Presenting the Prospect of Direct Benefit to the Individual Subjects (45 CFR 46.405)

Research in which more than minimal risk is presented to children by an intervention or procedure, but which holds the prospect of direct benefit to individual subjects, may be approved by an IRB provided it has determined that:

(i) the conditions of section C-1 (above) are met;

(ii) the relationship of the anticipated benefit to the risk is at least as favorable to the subjects as that presented by

available alternative approaches;

(iii) such risk is justified by the anticipated benefit to the subjects;

(iv) adequate provisions are made for soliciting the assent of the children and the permission of their parents or guardians, as set forth in C-3.

Examples of research that fall into this category might include experimental drug treatment for a childhood disease or condition when data exist which indicate a prospect for direct benefit to the individual child participant. The key idea in this category is that the intervention or procedure must provide a prospect for direct benefit to the child, not merely incidental benefit from having participated in a research activity.

(c) Category 3: Research Involving Greater Than Minimal Risk and No Prospect of Direct Benefit to the Individual Subjects (45 CFR 46.406)

Research involving greater than minimal risk to children and no prospect of direct benefit to the individual subjects, may be approved by an IRB if it has determined that:

(i) the conditions of section C-1 (above) are met;

(ii) such risk represents a <u>minor</u> increase over minimal risk;

(iii) the intervention or procedure presents experiences to the child subjects that are reasonably commensurate with those inherent in their actual, or expected medical, dental, psychological, social, or educational situations;

(iv) the intervention or procedure is likely to yield generalizable knowledge about the subject's disorder or condition which is of vital importance for understanding or amelioration of the disorder or condition;

(v) adequate provisions are made soliciting the assent of the child and the permission of their parents or guardians, as set forth in section C-3 (below).

Examples of research that fall into this category might include biomedical sample gathering for the purpose of learning about (but not treating) a childhood disease or condition, stressful educational tests to determine the basis for developing practical methods of teaching children with certain characteristics, and behavioral manipulations designed to elicit an understanding of a childhood psychological condition. In each of these examples the research provides the child subject with no direct benefit, but may provide vital information about the disorder/condition with only minor increases of risk to the subject. Moreover, the research experiences reasonably resemble those the child might encounter in actual medical, educational, and psychological settings.

(d) Category 4: Research Not Otherwise Approvable (45 CFR 46.407)

Research that is not otherwise approvable under one of the above categories [(a), (b), and (c), above] may be evaluated by an IRB and determined to present a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children. In these cases the IRB will forward the research study through the Director, Office of Human Subjects Research, NIH, to the Secretary, Department of Health and Human Services. The Secretary of DHHS, after consultation with a panel of experts from relevant disciplines and after providing opportunity for public review and comment, must determine that in fact the research falls into one of the three above categories, or that it meets the following provisions:

(i) the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious child health or welfare problem;

(ii) the research will be performed in accordance with sound ethical principles;

(iii) the research makes adequate provisions for soliciting the children's assents and the permissions of their

parents or guardians, as set forth in the next section.

3. Requirements for Permission by Parents or Guardians and for Assent by Children

The IRB shall also determine that adequate provisions are made for:

(a) soliciting the assent of the children (when in the determination of the IRB, they are capable of assent, see Section D, below) and the permission of their parents or guardians;

(b) considering the objections to participation by a child who is capable of assent. A child's objection(s) should be binding unless the intervention holds out a prospect of benefit that is important to the health or well-being of the child and that is available only in the context of research;

(c) monitoring the solicitation of assent and permission when appropriate, and providing opportunities for at least one parent or guardian to assist in the conduct of the research procedures (for example, allowing the parent to be present when blood tests and/or other research procedures are performed);

(d) when parental permission is to be obtained, the IRB may find that the permission of <u>one</u> parent is sufficient for research to be conducted under sections C-2(a) and C-2(b) (categories 1 and 2, above). When research is covered by sections C-2(c), C-2(d) (categories 3 and 4, above), and permission is to be obtained from parents, <u>both</u> parents must give their permission unless one parent is deceased, unknown, legally incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child;

(e) if the IRB determines that a research protocol is designed for conditions or a subject population for which parental or guardian permission is not a reasonable requirement to protect the subjects, (e.g., neglected or abused children), it may waive such a requirement provided an appropriate mechanism for protecting the children research subjects is

substituted. The choice of an appropriate mechanism should depend upon the nature and purpose of the research activities described in the protocol, the risk and anticipated benefit to the research subjects, their age, maturity, status and condition.

4. Wards

(a) Children who are wards of the State or any other agency, institution, or entity may participate in research described in sections C-2(a) and C-2(b) (categories 1 and 2, above).

(b) They may participate in research of greater than minimal risk with no direct benefit to individual subjects (C-2(c) or C-2(d)) only if:

(i) the research is related to their status as wards; or

(ii) the research will be conducted in a setting where the majority of children involved as subjects are not wards.

(c) If research to be conducted under section C-4 (b) is approved, an advocate shall be appointed for each child, in addition to any other individual acting as guardian or *in loco parentis* for the child. One individual may act as advocate for more than one child.

(d) Individuals may not serve as advocates if they:

(i) have any financial interest in, or other association with, the institution conducting or sponsoring the research; or

(ii) have any financial interest in, or other association with, that State, agency, institution, or entity of which the subject is a ward.

D. APPROACH TO A CHILD'S ASSENT

This section is intended to aid investigators in obtaining a child's assent to research. Although a child, as a research subject, maintains a limited capacity for self-determination, this ought not

preclude the researcher from seeking assent, thereby respecting the child as a person.

1. Policy on Obtaining Child's Assent

Every protocol involving children shall include a discussion of how assent will be obtained for that particular study. This may take the form of a description of how information will be verbally communicated to the child or a sample written assent document appropriate to the age and comprehension level of the children to be enrolled. A written assent should be obtained when, in the determination of the IRB, in consultation with the principal investigator, it is determined to be a meaningful process within the context of the particular research study. If the IRB determines under Section C paragraph 3, that children in a particular protocol are not capable of assent, then the protocol shall include an explication of the reasons for that determination.

The investigator is obligated to justify each instance when assent (written or oral) is not possible.

(a) In determining whether children are capable of giving meaningful assent, the IRB shall take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in a particular research study, or for each child, as the IRB deems appropriate.

(b) The assent of children research subjects is not required in the infrequent circumstances in which the IRB determines that:

(i) some or all of the children are so limited that they cannot reasonably be consulted, or

(ii) the intervention or procedure holds out a prospect of direct benefit that is important to the health or well-being of the individual child and is available only in the context of research.

(c) If assent is obtained verbally, this should be documented on the protocol consent form signed by the parents/guardians (see attachment A).

(d) When a written assent document is used, the signatures of the parents/guardians and a witness should be obtained in addition to that of the child (see attachment B).

2. Guidelines

The following guidelines are intended to assist the investigator and the IRB to formulate assent procedures that will best serve the needs of the children who participate in that protocol.

(a) Critical to the assent process is consideration of the maturation level of the children's thought processes and capacities for comprehension:

(i) A child with normal cognitive development becomes capable of meaningful assent at about the age of 7 years, although there is a wide range of variation.

(ii) Time is not similarly comprehended at all ages. A discussion of time requirements in a research protocol must be appropriate to the child's level of understanding.

(iii) Age is only a gross index of mental level and reasoning capacity.

(iv) A child's level of comprehension and reasoning will be altered by states of anxiety, and physical and emotional disturbances.

(b) The protocol should be explained in such a manner that the child can provide a meaningful and informed assent. This explanation should include:

(i) A reason for the child being at the research facility; i.e., relate the child's presence at the hospital to something meaningful in his/her experience.

(ii) Realistic expectations concerning what a child will experience in the hospital, including:

staying in bed....or not

going home....or staying in the hospital
separation from the parents/friends .... or not
supervision by doctors and nurses
presence of other patients

(iii) A description of specific procedures and the immediate consequences of those procedures, e.g., pain, falling asleep, medication by a tube put into the arm, how the child will look different or how his/her body might be changed as result of participation in the study, etc.

(iv) An explanation of the reason for the study and the hoped for benefits to the child, or how the study accomplishes benefits for other children.

(c) Children involved in research which holds no anticipated benefit to them as individuals [see sections C-2(a), C-2(c) and C-2(d)] may withdraw or choose not to participate in the study at all. Since children (to age 7, for example) may not be accustomed to this type of control over what they are permitted to do, this right to dissent, if granted, may be misinterpreted. It is the investigator's responsibility to guide both the child and parents/guardians in this decision.

ATTACHMENT A

When the child's assent is obtained verbally, the following statement should be added to the protocol consent form:

> The information in the above consent form has been adequately described to my child by Dr. _____ in language that this child can understand. My child willingly agrees to participate in this research project.

The signatures of the parent/guardian, witness, and investigator should be obtained on this form as with all other consent documents.

ATTACHMENT B

Example (10 year old, non-therapeutic research)

The NIH has a hospital in which doctors study many diseases.

The doctors at the National Institutes of Health want to understand why some children become sick more easily than normal.

In order to do this, we need to do tests on normal children so that the problems in sick children can be understood.

We are asking that you help with the following tests. In order to collect the specimen properly we will ask you to spend two nights and days in the hospital. During that time
you will be able to walk around the ward, except when you are having tests.

The tests involve:

> blood tests to be taken from your arm each morning. These may hurt for a moment, or may bleed for a moment, but that stops quickly.
>
> We will ask you to collect urine for 2 whole days in a large jar. On the second day we will place a plastic tube in one of the veins in your hand and will give you a fluid, containing "hormones" or body chemicals which act on the tonsils. You will experience some pain when the plastic tube is inserted, but that only lasts a minute.

Your parents or friends may visit you each day when you are in the hospital.

Please ask the doctors and nurses if you have any questions. You may not want to continue the project and may stop at anytime, however, you are helping provide information that may help other sick children and because of that we want you to finish the tests if at all possible.

I have had the tests explained to me and have had the opportunity to ask questions.

Signature	Witness
Parent/Guardian	Date
Investigator	